

39. (Reiterated.) A method for treating a disorder which is associated with increased expression of the polypeptide of claim 18 comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition comprising an antagonist which specifically binds to and inhibits the activity of said polypeptide.

40. (Reiterated.) A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 18, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 18 to a compound, and
- b) detecting agonist activity in the sample.

41. (Reiterated.) A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 18, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 18 to a compound, and
- b) detecting antagonist activity in the sample.

42. (Reiterated.) A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 21, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

REMARKS

Claims 18-42 are pending in the application. Claims 20-32 and 35-42 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claim 18 has been amended to clarify the subject of the claimed invention. Support for the additional claim limitations of claim 18 is found in the specification at page 13, lines 10-11, where variants having at least 95% amino acid sequence identity to the amino acid sequence of CYSTAR are disclosed; at page 48, lines 5-19 where an assay for CYSTAR activity,

measured as the induction of increased CYSTAR expression by TCDD is described; and at page 7, line 8, page 28, line 24 through page 29, line 2, where the specification describes methods of screening antibodies for desired specificities. No new matter is added by these amendments. Entry of these amendments is respectfully requested. Therefore, claims 18, 19, 33 and 34 are currently being examined on the merits.

Information Disclosure Statement:

Applicants thank the Examiner for entering the dates of references 14 and 20 in the form 1449.

With respect to references 1-2 and 15-18, Applicants' records show that these references were provided in an Information Disclosure Statement for the parent application (08/822,264), that was mailed October 29, 1998. The information disclosure statement, form 1449 and the set of six references were mailed together with the issue fee transmittal and were received at the USPTO on November 2, 1998 according to the stamped date on the return receipt postcard. These references should therefore be found in the application file for the parent application, 08/822,264.

Rejections under 35 U.S.C. 101

Claims 18-19 and 33-34 are rejected under 35 U.S.C. 101 as allegedly lacking either a substantial asserted utility or a well established utility. In particular, the Examiner asserts that since "the function of the protein is not known, the protein lacks well established utility." (Office Action, page 5). In addition, the Examiner states that while the specification discloses the asserted utility of using the polypeptide in treating disorders associated with aberrant cellular development, differentiation, and inflammation, there is "no nexus between the unknown properties of the polypeptide and the treatment of the disease" and thus the treatment of diseases lacks substantial utility.

Applicants respectfully traverse, pointing out that the rejections are based solely upon the unfounded assertion that the claimed polypeptide has no known function. Applicants respectfully direct the Examiner's attention to the specification at page 12, wherein it is disclosed that the claimed polypeptide (CYSTAR) shares 79% amino acid identity with rat 25-Dx protein, which is known to be responsive to dioxin. Expression of 25-Dx in liver was enhanced in a dose dependent fashion over a

wide range of dioxin exposures. The rat 25-Dx protein was suggested to be a member of the cytokine/growth factor/prolactin receptor superfamily (see the specification, page 2, lines 4-22). CYSTAR and rat 25-Dx protein have similar hydrophobicity plots (Figures 3A and 3B). CYSTAR also has 93% identity with porcine steroid membrane binding protein, which binds to progesterone. In addition, CYSTAR contains a potential transmembrane domain. Based on this evidence, one of skill in the art would reasonably believe that CYSTAR is a cytokine/steroid receptor protein; in particular, that it is the human membrane bound progesterone receptor.

In the face of this evidence, the Examiner asserts that the claimed polypeptide is a receptor for which the function is not known. While acknowledging that the closest prior art (Falkenstein et al.) teaches that the protein binds progesterone, the Examiner claims that since "the protein is not the traditional progesterone steroid receptor which translocates to the nucleus which is well known", "the protein is only identified by binding characteristic [sic] which does not reveal its function." See Office Action, pages 4-5. The Examiner appears to be arguing that the claimed polypeptide (as well as the homologous protein of Falkenstein et al.) might be random proteins that happen by chance to bind progesterone. This conclusion is strongly contradicted by both the cited reference and the known art at the time. At the time of filing, it was well known in the art that certain steroid effects occurred too rapidly to be caused by nuclear translocation and transcriptional modulation. These rapid non-genomic steroid effects were understood to be due to a distinct class of membrane-bound steroid receptors, since "specific binding sites have been described in membranes for various steroids exposing pharmacological properties distinct from those of the intracellular receptors" (Falkenstein et al., page 86). The Examiner's attention is also respectfully directed to the specification, page 3, and the enclosed reference (M. Wehling, (1997) "Specific, nongenomic actions of steroid hormones" Ann. Rev. Physiol. 59:365-393).

In particular, at the time of filing progesterone was known to cause nongenomic actions including effects on oocyte maturation and the spermatozoan acrosome reaction (Wehling, page 375). Membrane binding sites for progesterone had been identified on both oocyte and sperm membranes (Wehling, pages 380-381). Progesterone nongenomic action was also known to have effects on reproductive behavior, and as an anesthetic (Wehling, page 384). Thus, in contrast to the Examiner's

assertions, there is a clear nexus between the function of CYSTAR and reproductive/developmental disorders. Furthermore, as discussed in Wehling (page 386), possession of steroid membrane receptors was well known to be potentially useful in allowing researchers “to devise agonists; to search for antagonists; to study proximal parts of signaling”.

An additional use for CYSTAR is in expression profiling. In recent years, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. The amino acid sequences of expressed polypeptides or polypeptide fragments are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29 (7):655, 656 (1999):

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra*. Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes

include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray, including cell cycle control genes). Note in particular that the sequences of the claimed invention are included in this list of particularly important classes of genes for toxicology testing. CYSTAR is a homolog of rat 25-Dx protein which is known to be responsive to dioxin. As such, CYSTAR and the sequences encoding it are of particular use in testing potential new drugs for toxicity, since CYSTAR is already known to be responsive to one prominent toxin.

Based upon the above evidence, it is clear that one of skill in the art would conclude that the claimed CYSTAR polypeptides and compositions thereof would have specific, real-world utilities both in the study of progesterone function through membrane-bound receptors, the treatment of reproductive and developmental disorders associated with progesterone action, and in toxicology testing. Withdrawal of the rejection of claims 18-19 and 33-34 under 35 U.S.C. 101 is therefore respectfully requested.

Claims 18-19 and 33-34 were also rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention (Office Action, page 6). The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Rejections under 35 U.S.C. 112, first paragraph:

Claims 18 and 33 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not sufficiently described in the specification so as to convey that the inventors had possession of the claimed invention at the time of filing. In particular, the Examiner asserts that the claimed genus of sequences having at least 90% amino acid identity to SEQ ID NO:1 is not sufficiently described as Applicants have not described the common attributes of the genus (Office Action, page 7). In order to clarify the intended subject matter of the claim, claim 1 has been amended to recite a

naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1, wherein said amino acid sequence encodes a polypeptide whose expression is upregulated by TCDD. Support for this additional claim limitation is found in the specification at page 48, lines 5-19 where an assay for CYSTAR activity, measured as the induction of increased CYSTAR expression by TCDD is described. Applicants also note that support for the limitation that the claimed sequences have at least 95% amino acid sequence identity to SEQ ID NO:1 is found in the specification at page 13, lines 10-11. The fact that a few of the amino acids in SEQ ID NO:1 are not specifically identified therefore does not prevent an adequate description of the genus, since the genus is now defined to include only those naturally occurring variants of SEQ ID NO:1 which retain the recited activity. In light of these amendments, one of skill in the art would reasonably understand what was encompassed by the claims and that Applicants were in possession of the claimed invention at the time of filing.

The Examiner also asserts that claim 18 limitation (b), which recites a naturally-occurring amino acid sequence having at least 90% (now amended to 95%) sequence identity of SEQ ID NO:1 is new matter because the subgeneric invention of naturally occurring variants is not disclosed in the specification. Applicants respectfully direct the Examiner's attention to the specification at page 5, lines 27-29, which explain that the term "amino acid sequence" may refer to either naturally occurring or synthetic molecules; and at page 36, lines 1-8, wherein the specification describes probes capable of identifying naturally occurring sequences encoding CYSTAR, alleles, or related sequences. These disclosures, together with the well-known concept of naturally occurring variants, clearly describe the genus of claim 18 (b). Thus, withdrawal of the rejections of claims 18 and 33 under 35 U.S.C. is therefore respectfully requested.

Rejections under 35 U.S.C. 102:

Claims 18 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Friedberg et al. Friedberg et al. disclose a CYP2B12 which has a 4 amino acid sequence identical to SEQ ID NO:1. Claims 18 and 33 are also rejected as being anticipated by Meyer et al. as evidenced by Falkenstein et al. Meyer et al. disclose a porcine progesterone binding protein. The Examiner alleged that this protein inherently has the sequence taught by Falkenstein et al., which has 93% amino acid sequence identity to

SEQ ID NO:1. Claims 18 and 33 are also rejected as being anticipated by Jacobs et al. US 5,976,837, who disclose a porcine progesterone membrane binding protein which has 93% amino acid identity to SEQ ID NO:1.

Applicants note that claim 18 (b) has been amended, as described above, to claim sequences having 95% amino acid identity to SEQ ID NO:1 instead of 90% as originally written. Thus the sequences of Meyer et al., Falkenstein et al., and Jacobs et al., which have only 93% identity to SEQ ID NO:1, no longer anticipate this claim.

It is well settled in patent law that a reference is anticipating under 35 U.S.C. § 102 (b) only if all elements of the claimed invention are disclosed in the reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994). Claim 18 has also been amended to add additional limitations not met by the reference fragments. Claim 18 now recites a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said fragment encodes a polypeptide whose expression is upregulated by TCDD, and an immunologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1. Support for the additional claim limitations of claim 18 is found in the specification at page 48, lines 5-19 where an assay for CYSTAR activity, measured as the induction of increased CYSTAR expression by TCDD is described; and at page 7, line 8, and at page 28, line 24 through page 29, line 2, where the specification describes methods of screening antibodies for desired specificities. Fragments of reference sequences do not meet the limitation of “immunologically active” as defined in the amended claims, as fragments of a sequence having only 93% identity to SEQ ID NO:1 (or less, as for the peptide of Friedberg et al.) cannot be used to generate antibodies that specifically bind to SEQ ID NO:1. Nor do fragments of the claimed sequence meet the limitations of the “biologically active” fragments, since the fragments of the reference proteins have not been shown to be upregulated in expression by TCDD. In particular, there is no evidence presented by the Examiner that demonstrates that the sequence of Friedberg et al., which is a cytochrome actually has any of the disclosed biological activities of CYSTAR. Withdrawal of the rejection of claim 18 and dependent claim 33 under 35 U.S.C. 102(b) as anticipated by Friedberg et al., Meyer et al. as evidenced by Falkenstein et al., and Jacobs et al. is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.


Pursuant to the attached Petition For Extension of Time, the Commissioner is hereby authorized to charge the fee of **\$110.00**, or any additional fee that may be required, or credit any overpayment to Incyte Genomics, Inc. Deposit Account No. **09-0108**.

This form is enclosed in duplicate.

Respectfully submitted,

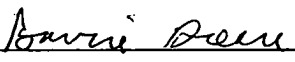
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